REMARKS

Claims 1 – 6, 22, 24, 26, 27, 35, and 36 are currently pending. Claims 1, 22 and 24 are the pending independent claims. In the Office Action, the Examiner first objected to the priority claim in the specification. Claims 1 – 7, 24 – 27, 35, and 36 were rejected under Section 112, second paragraph as allegedly being indefinite. On the merits, the Examiner made the following prior art rejections:

1. Claims 1 – 7, 22, 23, 35, and 36 were rejected und Section 102 (b) as allegedly anticipated by U.S. Patent No. 5,229,382 to Chakrabarti et al. (Chakrabarti '382).

2. Claims 1 – 7, 22, 23, 35, and 36 were rejected und Section 102 (b) as allegedly anticipated by U.S. Patent No. 6,008,216 to Chakrabarti et al. (Chakrabarti '216).

3. Claims 1 – 7, 35, and 36 were rejected und Section 102 (e) as allegedly anticipated by U.S. Patent No. 7,329,747 to Keltjens et al. (Keltjens '747).

4. Claims 1 – 7, 22 – 24, 35, and 36 were rejected und Section 102 (e) as allegedly anticipated by U.S. Patent No. 7,459,449 to Keltjens et al. (Keltjens '449).

5. Claims 1 – 7, 22 – 27, 35, and 36 were rejected und Section 102 (e) as allegedly anticipated by U.S. Patent Application Publication No. 2005/0272720 to Keltjens et al. (Keltjens '720).

Each of the foregoing rejections is respectfully traversed and favorable reconsideration is requested in view of the above amendments and following remarks.

I. Priority Claim.

The Examiner first objected that a reference to the priority applications needed to be inserted as the first sentence in the specification. In response, page 1 of the application is herein amended to make an appropriate reference to both the PCT application and the earlier Slovenian priority applications. However, since the priority applications were noted in the Application Data Sheet submitted with the national phase entry, it submitted that no petition and associated fee is required with this amendment and, in fact, the amendment is technically not required, although Applicants have no objection to including a reference to the PCT and Slovenian applications pursuant to the Examiner's request to make the priority claim even more evident.

II. Indefiniteness Rejections.

The Examiner next contends that Claims 1 – 7, 24 – 27, 35, and 36 are indefinite. The indefiniteness of these claims is alleged to derive from the misspellings of the words "olanzopine" in Claim 1, "imethyl" in Claim 6, and "N-desmethylolanzopine" in Claim 24 and from the phrase "such as" in Claim 24.

In response to these rejections, "olanzopine" has been changed to olanzapine in Claim 1 and "imethyl" has been changed to dimethyl in Claim 6. In Claim 24, "N-desmethylolanzopine" has been changed to N-desmethylolanzapine and the limitation "such as" has been deleted from the claim. In view of these amendments, it is submitted that any alleged indefiniteness issues have been overcome, and that the Section 112 rejections should accordingly be withdrawn.

III. Prior Art Rejections of Claims 1 – 7, 35, and 36.

The Examiner argues that Claims 1 – 7, 35 and 36 are anticipated by Chakrabarti '382, Chakrabarti '216, Keltjens '747, Keltjens '449 and Keltjens '720. It is respectfully submitted that none of these rejections are well taken, and that all should be withdrawn.

Claim 1 is directed to a purification process for olanzapine wherein, among other things, free form olanzapine is mixed with an acid and converted to an acid addition salt. The acid addition salt is precipitated and isolated. Then, the olanzapine acid addition salt is transformed to free form olanzapine. Thus, the method begins and ends with free form olanzapine.

As amended herein,[1] Claim 1 more particularly states, among other things, that the transformation of the acid addition salt back to free form olanzapine comprises: (1) dissolving an acid addition salt of olanzapine in water to form an aqueous solution thereof, (2) adjusting the pH of the obtained solution to about 8-10, (3) extracting olanzapine from the water phase to an organic solvent phase and (4) isolating the acid addition salt of olanzapine from the organic solvent phase by concentrating the solution and separation of crystals of the aforementioned salt of olanzapine therefrom.

The Examiner cites to identical language in both of the Chakrabarti references, but this language fails to anticipate the subject matter of Claim 1. Both Chakrabarti references simply

[1] Claim 7 has been cancelled in view of the current amendments to Claim 1.

state that olanzapine may be converted into an acid addition salt and then speculate that the acid addition salt may be used "in purification"; however, Chakrabarti fails to disclose or suggest any actual process steps for purification of olanzapine via the acid addition salt. Conclusary generalized speculation of this sort cannot properly be said to anticipate specifically delineated steps for carrying out a method. The bottom line is that neither of the Chakrabarti references discloses or suggests the claimed steps of the purification method as called for in Claim 1 within their "four corners." Thus, neither reference can properly be said to anticipate the claim.

Turning to the Keltjens references, the disclosure of Keltjens '747 is similar to that of the Chakrabarti references discussed above. Keltjens '747 discloses what is said to be the conversion of free form olanzapine into an acid addition salt; however, Keltjens '747 fails to disclose or suggest specific process steps for purification of olanzapine via the acid addition salt. In particular, Keltjens '747 does not disclose or suggest the purification method steps as called for in Claim 1.

The Keltjens '449 patent discloses what is said to be the reaction of olanzapine with benzoic acid and the formation of the benzoate acid addition salt in Examples 16 B and 16 D, as cited by the Examiner. However, Keltjens '449 does not disclose or suggest transformation of these acid addition salts back to free form olanzapine as called for in Claim 1. Finally, the Keltjens '720 application mentions what is said to be the reaction of olanzapine with acetic acid and the formation of the acetate acid addition salt in Examples 4 and 6 cited by the Examiner. However, Keltjens '720 does not disclose or suggest transformation of these acid addition salts back to free form olanzapine as called for in Claim 1.

In view of the foregoing, it is submitted that the subject matter of Claim 1 (and that of each its dependent claims) cannot properly be said to be anticipated by either Chakrabarti '382, Chakrabarti '216, Keltjens '747, Keltjens '449, or Keltjens '720. Again, none can fairly be said to disclose within its "four corners" all steps of the claimed process. Accordingly, the anticipation rejections based thereon are not well taken and should be withdrawn.

IV. Prior Art Rejections of Claims 22 and 23.

Claims 22 and 23 are said to be anticipated by Chakrabarti '382, Chakrabarti '216, Keltjens '449, and Keltjens '720.

As amended herein,[2] Claim 22 is directed to a method for making olanzapine by, among other things, reacting 4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine hydrochloride with N-methylpiperazine to yield free form olanzapine and then transforming the free form olanzapine into an acid addition salt. The steps of the method specify that, among other things, the free form olanzapine is transformed to an acid addition salt form according to the following substeps:

i) the obtained reaction mixture is diluted with water,

ii) the diluted reaction mixture is extracted with an organic solvent, wherein the organic solvent is selected from the group consisting of ketones, chlorinated hydrocarbons, and mixures thereof,

iii) the organic phase is evaporated and the residue is diluted with a second solvent to obtain a solution containing the residue,

iv) an organic acid is added to the solution containing the residue to precipitate olanzapine acid addition salt therefrom and

v) precipitated olanzapine acid addition salt is isolated by formation and separation of crystals from the solution.

Thus substep (ii) of method called for in Claim 22 specifies, among other things, the use of ketones and /or chlorinated hydrocarbons in the initial separation and extraction of the olanzapine.

At least the above substep is very plainly neither disclosed nor suggested in any of the four cited references (Chakrabarti '382, Chakrabarti '216, Keltjens '449, and Keltjens '720). None of these references teaches formation of olanzapine by reaction of 4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine hydrochloride with N-methylpiperazine, followed by the use of ketones and /or chlorinated hydrocarbons in the initial separation and extraction of the olanzapine, according to Claim 22. Thus, the subject matter of Claim 22 cannot properly be said

[2] Claim 23 has been cancelled in view of the current amendments to Claim 22.

to be anticipated by Chakrabarti '382, Chakrabarti '216, Keltjens '449, or Keltjens '720. Accordingly, the anticipation rejections based thereon are also not well taken and should be withdrawn.

V. Prior Art Rejections of Claims 24 – 27.

Finally, the Examiner argues that Claim 24 is anticipated by Keltjens '449 and that Claims 24 – 27 are anticipated by Keltjens '720.

In its present amended form,[3] Claim 24 is directed to a method for making olanzapine in the form of an acid addition salt. The steps of the method specify that, among other things:

a) N-desmethylolanzapine is reacted with a methylating agent to yield olanzapine,

b) the obtained reaction mixture is diluted with water and acidified with an acid,

c) to the reaction mixture, a *chlorinated organic solvent* is added to provide separable aqueous and organic phases which are then separated,

d) the obtained aqueous phase is neutralized and olanzapine is extracted therefrom with a *chlorinated organic solvent* to obtain the organic solvent phase.

The totality of all the method steps called for in Claim 24, including at least steps (c) and (d) of the method, which specify at least the use of a chlorinated organic solvent in the initial separation and extraction of the olanzapine, are very plainly not disclosed or suggested in Keltjens '449 or Keltjens '720 references. Further, neither reference teaches the formation of olanzapine by reaction of N-desmethylolanzapine with a methylating agent, follow by the use of a chlorinated organic solvent in the initial separation and extraction of the olanzapine, according to Applicants' claims.

Thus, all the steps called for in Claim 24 (nor "all" of those of each its dependent claims) are not disclosed in the "four corners" of either Keltjens '449 or by Keltjens '720. Accordingly, the anticipation rejections based thereon are not well taken and should be withdrawn.

In light of the foregoing, Applicants urge the Examiner to reconsider the application, to withdraw all objections/ rejections, and to issue a Notice of Allowance at the earliest possible convenience.

[3] Claim 25 has been cancelled in view of the current amendments to Claim 24.

In the event this response is not timely filed or any other matter involving the need for a petition is believed to be required in connection with this response, Applicants hereby petition for an appropriate extension of time or for the needed relief or matter required. The fee for any needed extension, or for any other matter believed to be required to be addressed by petition, along with any other fees which may be due with respect to this response, may be charged to our Deposit Account No. 12-2355.

Respectfully submitted,

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